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(71) Applicant: AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralda Farms, Madison, NJ 07940-0874 (US).

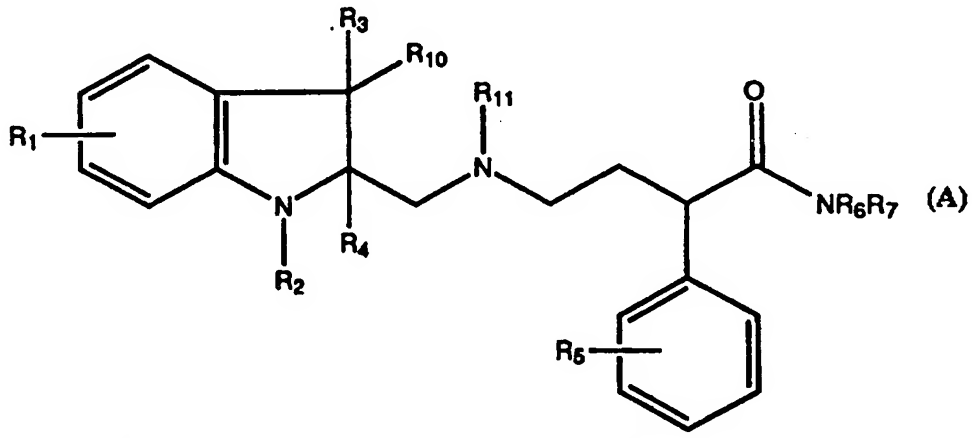
(72) Inventors: COMMONS, Thomas, Joseph; 397 Drummers Lane, Wayne, PA 19087 (US). LACLAIR, Christa, Marie; 54 Ardsley Court, Newtown, PA 18940 (US). CHRISTMAN, Susan; 2905 Forest Haven Boulevard, Edison, NJ 08817 (US).

(74) Agents: ALICE, Ronald, W.; American Home Products Corporation, Five Giralda Farms, Madison, NJ 07940-0874 (US) et al.

(54) Title: INDOLE DERIVATIVES USEFUL AS SEROTONERGIC AGENTS

(57) Abstract

The compound of formula (A), where R_1 and R_5 are independently hydrogen, fluorine, chlorine, bromine, iodine, trifluoromethyl, cyano, nitro, CO_2H, C_1-C_6 alkyl, C_2-C_{10} alkenyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkyl, cycloalkylalkyl, C_3-C_8 cycloalkyloxy, C_2-C_7 alkylcarbonyl, C_2-C_7 alkylcarbonyloxy, C_2-C_7 alkoxycarbonyl, mono- or di-alkylaminocarbonyl, tetrazolyl, -OH, $-(CH_2)_{1-6}OH$, -SH, $-NH_2$ or $-(CH_2)_{1-6}NR_8R_9$ where R_8 is hydrogen, C_1-C_6 alkyl, C_2-C_7 alkylcarbonyl, C_2-C_7 alkoxycarbonyl and R_9 is hydrogen or C_1-C_6 alkyl; R_{10} and R_{11} together represent dimethylene whilst R_2 is hydrogen or C_1-C_6 alkyl or R_2 and R_{11} together represent dimethylene whilst R_{10} is hydrogen; R_3 and R_4 are hydrogen or taken together with the carbon atoms to which they are attached form a double bond; R_6 and R_7 are independently H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_8 cycloalkyl, cycloalkylalkyl or R_6 and R_7 taken together are polymethylene, which, with the nitrogen atom to which they are attached, form a ring of 3 to 8 atoms; or a pharmaceutically acceptable salt thereof is useful as a serotonergic agent.



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INDOLE DERIVATIVES USEFUL AS SEROTONERGIC AGENTS

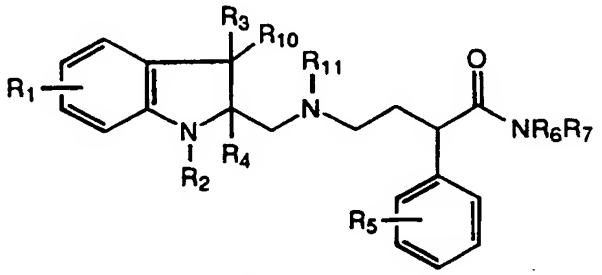
Background of Invention

The compounds of this invention possess high affinity for the serotonin 5-HT_{1A} receptor and as such are useful as antidepressant and anxiolytic agents for the treatment of a variety of central nervous system disorders such as depression, anxiety, eating disorders, sexual disfunction, addiction and related problems. As an example buspirone (US Patent 3,717,634) is known to display potent affinity for the 5-HT_{1A} serotonin receptor. Buspirone is used extensively for the treatment of anxiety and this anxiolytic activity is believed to be due, at least partially, to its 5-HT_{1A} receptor affinity [VanderMaelen et al., Eut. J. Pharmacol. 1986, *129* (123-130)].

WO 9,311,122-A and US 4,988,814 exemplify piperazine derivatives as compounds with affinity for the 5-HT_{1A} receptor.

DESCRIPTION OF THE INVENTION

This invention relates to a series of novel compounds which are useful as pharmaceuticals and in particular have activity as serotonergic agents and have the general formula A,



A

where

R_1 and R_5 are independently hydrogen, fluorine, chlorine, bromine, iodine, trifluoromethyl, cyano, nitro, CO_2H, C_1-C_6 alkyl, C_2-C_{10} alkenyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkyl, cycloalkylalkyl where the alkyl group is of 1 to 6 carbon atoms and the cycloalkyl

group has 3 to 8 carbon atoms, C_3-C_8 cycloalkyloxy, C_2-C_7 alkylcarbonyl, C_2-C_7 alkylcarbonyloxy, C_2-C_7 alkoxycarbonyl, mono- or di- alkylaminocarbonyl in which each alkyl group, independently, contains 1 to 6 carbon atoms, tetrazolyl, OH, $-(CH_2)_{1-6}OH$, -SH, $-NH_2$ or $-(CH_2)_{1-6}NR_8R_9$ where R_8 is hydrogen, C_1-C_6 alkyl, C_2-C_7 alkylcarbonyl, C_2-C_7 alkoxycarbonyl and R_9 is hydrogen or C_1-C_6 alkyl;

R_{10} and R_{11} together represent dimethylene whilst R_2 is hydrogen or C_1-C_6 alkyl or R_2 and R_{11} together represent dimethylene whilst R_{10} is Hydrogen;

R_3 and R_4 are hydrogen or taken together with the carbon atoms to which they are attached form a double bond;

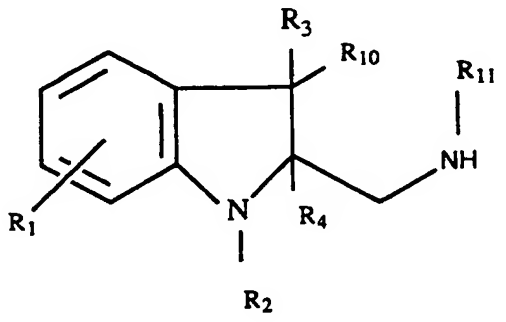
R_6 and R_7 are independently H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_8 cycloalkyl, cycloalkylalkyl where the alkyl group is 1 to 6 carbon atoms and the cycloalkyl group is 3 to 8 carbon atoms or R_6 and R_7 taken together are polymethylene, which, with the nitrogen atom to which they are attached, form a ring of 3 to 8 atoms; or a pharmaceutically acceptable salt thereof.

The compounds where R_{10} and R_{11} together represent dimethylene are Pyrido[3,4-b] indole derivatives. Those where R_2 and R_{11} together represent dimethylene are pyrazino[1,2-a] indole derivatives. Of both these kinds of compounds, a preferred group from the viewpoint of facile production and economic considerations, are those in which R_1 and R_5, independently, represent hydrogen, fluorine, chlorine, bromine, trifluoromethyl, CO_2H, C_1-C_3 alkyl, C_1-C_3 alkoxy, C_2-C_4 alkoxycarbonyl, mono- or di-alkylaminocarbonyl in which each alkyl group, independently, contains 1 to 6 carbon atoms, -OH, $-NH_2$ or $-(CH_2)_{1-3}NR_8R_9$ where R_8 is hydrogen or C_1-C_3 alkyl and R_9 is hydrogen or C_1-C_3 alkyl; R_2 is H or C_1-C_3 alkyl; R_3 and R_4 are hydrogen or taken together with the carbon atoms to which they are attached form a double bond; and R_6 and R_7, taken together are polymethylene, which, with the nitrogen atom to which they are attached, form a ring of 5 to 8 atoms; or a pharmaceutically acceptable salt thereof.

The pharmaceutically acceptable salts may be those derived from such organic and inorganic acids as: acetic, lactic, citric, tartaric, succinic, maleic, malonic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, and similarly known acceptable acids. Where the compounds of this invention contain acidic substituents such as the carboxylic acid group, salts may be formed with pharmaceutically acceptable bases to form alkali metal (such as Na, K or Li), alkaline earth metal (such as Ca or Mg), the ammonium or mono- or dialkylamine salts, the alkyl portion of said amine salts containing 1 to 6 carbon atoms.

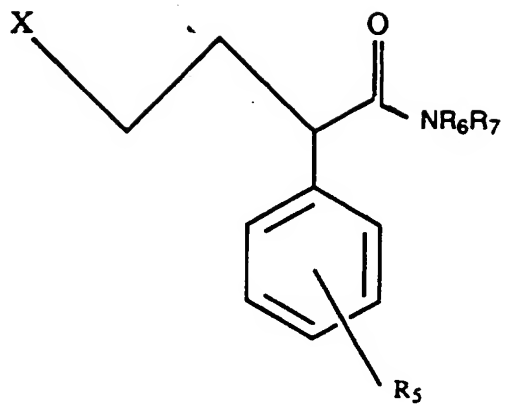
The compounds of this invention possess one or three chiral centers depending on the identity of R3 and R4. Therefore they present diastereoisomers and enantiomers, which may be separated by conventional procedures. In naming the compounds throughout this disclosure and in the appended claims it is to be understood that it is intended to embrace the isomers as their mixtures and in their pure form.

The compounds having formula A and their pharmaceutically acceptable salts may be prepared by process which comprises reaction of a compound having formula B



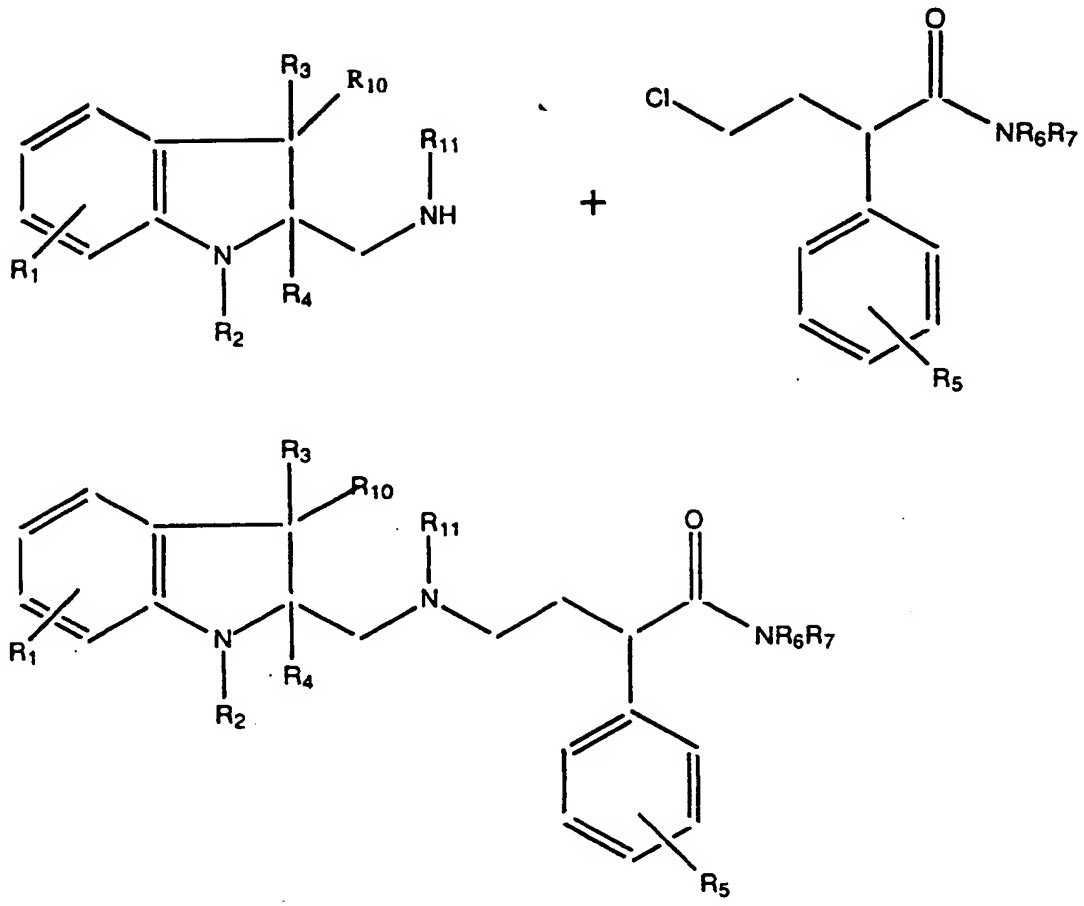
B

where R1, R2,R3,R4,R10 and R11 are as defined above with a compound having the formula C:



C

where X is a leaving group, for example, chlorine, bromine or methanesulfonyloxy and R5,R6 and R7 are as defined above and, where appropriate, converting a resultant compound havineg formula A into a pharmaceutically acceptable salt thereof. In particular the compounds of this invention are conveniently prepared by the route shown in the following scheme. Specific examples are given in the Experimental Section. These examples are for illustrative purposes only and are not to be construed as limitations for the disclosed invention. Those skilled in the art will be aware of other methods of preparing compounds of this invention. The starting materials or intermediates are available commercially or can be prepared by standard literature procedures.



High affinity for the serotonin 5-HT_{1A} receptor for the compounds of this invention was established by testing them in accordance with the standard pharmacological test procedure in which the compound's ability to displace [^{3}H] 8-OHDPAT (dipropylaminotetralin) from the 5-HT_{1A} serotonin receptor was determined following the procedure of Hall et al., J. Neurochem. 44 1685 (1985). This procedure is employed to analogize the properties of the claimed compounds with that of buspirone, which is a standard for anxiolytic activity, and, like the compounds of this invention, displays potent affinity for the 5-HT_{1A} serotonin receptor subtype. The anxiolytic activity of buspirone is believed to be, at least partially, due to its 5-HT_{1A} receptor affinity [VanderMaelen et al., Eur. J. Pharmacol. 1986, *129* (123-130)]. The results of this experimental test procedure are given in the following table:

TABLE

	5-HT_{1A} Binding (IC_{50})
Example 1	30.9 nM
Example 2	33.3 nM
Example 3	37.1 nM
Example 4	67.4 nM
Example 6	85.3nM

Hence, the compounds of this invention demonstrated high affinity for the serotonin 5-HT_{1A} receptor subtype, and are therefore useful in the treatment of multi-CNS disorders amenable to treatment with antidepressant and anxiolytic agents. The Pyride [3,4-b] indole derivatives are preferred.

Based upon this receptor binding data, the compounds of this invention are characterized as anxiolytic and/or antidepressant agents useful in the treatment of depression and in alleviating anxiety . The compounds may be administered orally or parentally. As such , the compounds may be administered neat or with a pharmaceutical carrier to a patient in need thereof. The pharmaceutical carrier may be solid or liquid. The invention therefore also provides a pharmaceutical composition comprising a compound having formula A or a pharmaceutically acceptable salt thereof in association or combination with a pharmaceutical carrier.

Applicable solid carriers can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintergrating agents or an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups and elixirs. The active ingredient of this invention can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fat. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples

of liquid carriers for oral and parenteral administration include water (particularly containing additives as above e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Oral administration may be either liquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

The dosage to be used in the treatment of a specific patient suffering from depression or anxiety must be subjectively determined by the attending physician. The variables involved include the specific state of anxiety or depression, and the size, age and response pattern of the patient.

EXAMPLE 1

1-Azepan-1-yl-2-phenyl-4-(1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl]-butan-1-one

A mixture of 1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (520 mg, 3.0 mmol), 1-(azepan-1-yl)-4-chloro-2-phenyl-butan-1-one (840 mg, 3.0 mmol), N,N-diisopropylethylamine (520 µl, 3.0 mmol) and potassium iodide (500 mg, 3.0 mmol) in 15 ml of anhydrous dimethylformamide was heated under nitrogen at 80°C for five hours. The reaction was partitioned between ethyl acetate and water. The aqueous layer was separated and the organic layer washed five times with water. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure to give 1.16 g of a brown oil. Purification of the oil on 200 g of silica gel (230-400 mesh) eluting with 75% ethyl acetate-hexane gave 441 mg of a solid foam. The foam was dissolved in diethyl ether containing a small amount of methylene chloride. To this solution was added 1.1 ml of 1N ethereal HCl. An oil precipitated, which after concentration of the supernatant liquid, solidified. The solid was collected by filtration and then recrystallized from isopropyl alcohol - ethanol to give 329 mg (22%) of the title compound as a light brown solid, hydrochloride, 0.375 isopropanolate, 0.375 ethanolate, mp 238-239°C.

Elemental Analysis for $C_{27}H_{34}ClN_3O \cdot 0.375\ C_3H_8O \cdot 0.375\ C_2H_6O$

Calc'd: C, 70.51; H, 8.04; N, 8.54

Found: C, 70.51; H, 7.86; N, 8.75

EXAMPLE 2

1-Azepan-1-yl-4-(9-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]-indol-2-yl]-2-phenyl-butan-1-one

A solution of benzyl chloroformate (8.3 ml, 58 mmol) in 20 ml of anhydrous tetrahydrofuran was added dropwise under nitrogen to a warm solution of 1,2,3,4-tetrahydro-9H-pyrido[3,4-b] indole (10.0 g, 58 mmol) and triethylamine (8.1 ml, 58 mmol) in 200 ml of anhydrous tetrahydrofuran. After the addition, the reaction was stirred at room temperature for four hours. The solvent was removed under reduced

pressure and the residue partitioned between ethyl acetate and 1N HCl. The organic layer was separated, extracted one time with 1N HCl, dried ($MgSO_4$) and the solvent removed under reduced pressure to give 15.7 g of an off-white solid. Recrystallization of the solid from 100 ml of 25% hexane-ethyl acetate gave 4.23 g (24%) of the benzyloxycarbonyl derivative of the starting material as a white solid. Recrystallization of the mother liquors from ethyl acetate-diisopropyl ether gave an additional 5.84 g (33%) of material, mp 102-104°C.

Elemental Analysis for $C_{19}H_{18}N_2O_2$

Calc'd: C, 74.49; H, 5.92; N, 9.14

Found: C, 74.44; H, 5.96; N, 9.30

Sodium hydride [1.5 g of a 60% oil dispersion (37 mmol)] was added in portions over fifteen minutes to a solution of the material prepared in the previous paragraph (9.5 g, 31 mmol) in 100 ml of anhydrous dimethylformamide under nitrogen at room temperature. After the addition was complete the reaction was stirred for three hours. Methyl iodide (5.8 ml, 93 mmol) was then added and the reaction stirred at room temperature overnight. The reaction was quenched by the slow addition of 1N HCl. The reaction was then partitioned between 1N HCl and ethyl acetate. The organic layer was separated, extracted three times with water, dried ($MgSO_4$) and the solvent removed under reduced pressure to give 10.4 g of a light yellow solid. Recrystallization of the solid from 100 ml of 20% ethyl acetate-diisopropyl ether gave 7.59 g (76%) of the 9-methyl derivative of the starting material as a white solid, mp 100-101°C.

Elemental Analysis for $C_{20}H_{20}N_2O_2$

Calc'd: C, 74.97; H, 6.29; N, 8.79

Found: C, 74.95; H, 6.30; N, 8.77

A mixture of the material prepared in the previous paragraph (4.0 g, 12 mmol) and 500 mg of 10% Pd/C in 40 ml of ethyl acetate was hydrogenated at room temperature and 40 psi for 5.5 hours. The catalyst was removed by filtration through celite and then rinsed thoroughly with ethanol and then dimethylformamide. The filtrate was concentrated under reduced pressure to give 2.39 g of an oil. The oil was dissolved in 15 ml of ethanol and 10 ml of 1N ethereal HCl was added. A solid

formed which was collected by filtration, rinsed with diethyl ether, and dried under high vacuum to give 2.23 g (80%) of 1,2,3,4-tetrahydro-9-methyl-pyrido[3,4-b]indole as the hydrochloride salt, mp > 250°C.

Elemental Analysis for $C_{12}H_{15}ClN_2$

Calc'd: C, 64.71; H, 6.79; N, 12.58

Found: C, 64.50; H, 6.73; N, 12.51

A mixture of the material prepared in the previous paragraph (1.56 g, 7.0 mmol), 1-(azepan-1-yl)-4-chloro-2-phenyl-butan-1-one (2.0 g, 7.0 mmol), N,N-diisopropylethylamine (2.4 ml, 14.0 mmol) and potassium iodide (1.2 g, 7.0 mmol) in 50 ml of anhydrous dimethylformamide was heated under nitrogen at 80°C for five hours and then left at room temperature overnight. The reaction was partitioned between ethyl acetate and water. The aqueous layer was separated and the organic layer washed five times with water. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure to give 2.89 g of a brown foam. Purification of the foam on 400 g of silica gel (230-400 mesh) eluting with 75% ethyl acetate-hexane gave 2.34 g of an off-white foam. The foam was dissolved in diethyl ether and to this solution was added 7 ml of 1N ethereal HCl. The solid formed was collected by filtration, rinsed with diethyl ether, and dried under high vacuum to give as a light yellow solid the title compound (2.00g, 58%) as a hydrochloride, hydrate, 0.08 diethyl etherate, mp 105-170°C.

Elemental Analysis for $C_{28}H_{38}ClN_3O_2 \cdot 0.08\ C_4H_{10}O$

Calc'd: C, 69.41; H, 7.98; N, 8.87

Found: C, 69.47; H, 7.78; N, 8.64

EXAMPLE 3

1-Azepan-1-yl-4-((trans)-9-methyl-1,3,4,4a,9,9a-hexahydro-2H-pyrido[3,4-b]indol-2-yl)-2-phenyl-butan-1-one

A mixture of 1,2,3,4-tetrahydro-9-methyl-pyrido[3,4-b]indole hydrochloride, prepared in the third paragraph of Example 2 (4.50 g, 20 mmol), potassium carbonate (14.0 g, 100 mmol) and benzyl chloride (2.3 ml, 20 mmol) in 45 ml of water plus 45

ml of tetrahydrofuran was stirred at room temperature overnight. The reaction was partitioned between water and ethyl acetate. The organic layer was separated, extracted one time with saturated sodium chloride, one time with water, dried ($MgSO_4$) and the solvent removed under reduced pressure to give 4.12 g of a yellow solid. Purification of the solid on 200 g of silica gel (230-400 mesh) eluting with hexane-ethyl acetate gave 3.67 g (66%) of the 2-benzyl derivative of the starting material as a white solid, mp 109-110°C.

Elemental Analysis for $C_{19}H_{20}N_2$

Calc'd: C, 82.57; H, 7.29; N, 10.14

Found: C, 82.29; H, 7.29; N, 10.01

A solution of 1M BH_3·THF (49.2 ml, 49.2 mmol) was added under nitrogen dropwise over ten minutes to a solution of the material prepared in the previous paragraph (3.63 g, 13 mmol) in 250 ml of anhydrous tetrahydrofuran at ice bath temperature. After the addition the cooling bath was removed and the reaction stirred at room temperature for thirty minutes and then refluxed for thirty minutes. After cooling to room temperature the solvent was removed under reduced pressure. To this residue 80 ml of one to one glacial acetic acid - 1N HCl was added cautiously. After the evolution of gas ceased the reaction was refluxed for fifteen minutes and then stirred overnight at room temperature. The reaction was again refluxed for forty-five minutes and then cooled in an ice bath before 50% aqueous NaOH was added until the reaction was basic. The reaction was extracted with methylene chloride, dried ($MgSO_4$) and the solvent removed under reduced pressure to give 5 g of a clear oil. Purification of the oil on 600 g of silica gel (230-400 mesh) eluting with 10% ethyl acetate - hexane gave 3.70 g of a white solid. Recrystallization of the solid from diisopropyl ether gave 2.61 g (71%) of the hexahydro derivative of the starting material as a white solid, mp 59-60°C.

Elemental Analysis for $C_{19}H_{22}N_2$

Calc'd: C, 81.97; H, 7.97; N, 10.06

Found: C, 81.84; H, 7.95; N, 10.05

A mixture of the material prepared in the preceding paragraph (2.48 g, 8.9 mmol) and 1.2 g of 10% Pd/C in 250 ml of absolute ethanol was hydrogenated at room temperature and 40 psi for 24 hours. The catalyst was removed by filtration

through celite and the filtrate concentrated to dryness under reduced pressure to give 1.49 g of a tan solid. Recrystallization of the solid from diisopropyl ether gave 617 mg (37%) of the debenzylated derivative of the starting material as an off-white solid, mp 68-70°C.

Elemental Analysis for $C_{12}H_{16}N_2$

Calc'd: C, 76.55; H, 8.57; N, 14.88

Found: C, 76.47; H, 8.68; N, 14.77

A mixture of the material produced in the previous paragraph (1.355 g, 7.2 mmol), 1-(azepan-1-yl)-4-chloro-2-phenyl-butan-1-one (2.0 g, 7.2 mmol), N,N-diisopropylethylamine (1.3 ml, 7.2 mmol) and potassium iodide (1.2 g, 7.2 mmol) in 30 ml of anhydrous dimethylformamide was heated under nitrogen at 80°C for five hours. The reaction was partitioned between ethyl acetate and water. The organic layer was separated, washed four times with water, dried ($MgSO_4$) and the solvent removed under reduced pressure to give 2.95 g of a brown solid. Purification of the solid on 300 g of silica gel (230-400 mesh) eluting with 50% hexane - ethyl acetate gave 2.30 g of an off-white solid. Recrystallization of the solid two times from isopropyl alcohol gave 0.542 g (17%) of the title compound as a white solid. NMR analysis of this material indicated it to be a single diastereomer, mp 111-113°C.

Elemental Analysis for $C_{28}H_{37}N_3O$

Calc'd: C, 77.92; H, 8.64; N, 9.74

Found: C, 77.52; H, 8.70; N, 9.63

The mother liquor from the above recrystallization was purified by HPLC (hexane-isopropyl alcohol) to give 169 mg of a yellow oil. The oil was dissolved in diethyl ether plus a small amount of CH_2Cl_2. One equivalent of 1N ethereal HCl was added and the solvent was concentrated to approximately half its volume. Diethyl ether was added and a solid formed. The solid was collected by filtration, rinsed with diethyl ether and dried under high vacuum to give 88.4 mg of a brown solid. NMR analysis indicated the solid to be the other diastereomer formed in the reaction, melting range 150-200 °C.

Elemental Analysis for $C_{28}H_{37}N_3O \cdot HCl \cdot 4H_2O \cdot 0.1\ C_4H_{10}O$

Calc'd: C, 62.30; H, 8.65; N, 7.67

Found: C, 62.81; H, 7.37; N, 7.60

EXAMPLE 4

1-Azepan-1-yl-4-((cis)-1,3,4,4a,9,9a-hexahydro-2H-pyrido[3,4-b]indol-2-yl)-2-phenyl-butan-1-one

Triethylsilane (27.8 ml, 174 mmol) was added under nitrogen to a solution of 1, 2, 3, 4-tetrahydro-9H-pyrido [3,4-b]indole (10.0 g, 58 mmol) in 150 ml of trifluoroacetic acid and the reaction stirred at 50°C for approximately five days. The solvent was removed under reduced pressure to give 96.88 g of a two phase oil. Purification of the oil by HPLC eluting with 2:1:1 ethyl acetate:methanol:ammonium hydroxide gave 3.83 g of the hexahydro derivative (trifluroacetic acid salt) of the starting material as a white solid, mp 146-149°C.

Elemental Analysis for $C_{11}H_{14}N_2 \cdot CF_3CO_2H$

Calc'd: C, 54.17; H, 5.24; N, 9.72.

Found: C, 54.26; H, 5.20; N, 9.70.

A mixture of the material produced in the previous paragraph (4.0 g, 14 mmol), 1-(azepan-1-yl)-4-chloro-2-phenyl-butan-1-one (3.89 g, 14 mmol), N,N-diisopropylethylamine (4.85 ml, 28 mmol) and potassium iodide (2.31 g, 14 mmol) in 250 ml of anhydrous dimethylformamide was heated under nitrogen at 75°C for six hours. The reaction was partitioned between ethyl acetate and water. The organic layer was separated, washed multiple times with water, dried ($MgSO_4$) and the solvent removed under reduced pressure to give 5.33 g of a brown oil. Purification of the oil by HPLC eluting with methanol-methylene chloride gave 1.14 g of a yellow oil. The oil was dissolved in diethyl ether containing a small amount of methylene chloride. One equivalent of ethereal HCl was added and the solid formed was collected by filtration and dried under high vacuum to give the title compound as a light brown solid, hydrochloride, hydrate, 0.2 diethyl etherate. NMR analysis and chiral HPLC showed the material to be a mixture of diastereomers and their enantiomers, mp 105-130°C.

Elemental Analysis for $C_{27}H_{35}N_3O \cdot HCl \cdot H_2O \cdot 0.2\ C_4H_{10}O$

Calc'd: C, 68.57; H, 8.28; N, 8.63.

Found: C, 68.51; H, 8.19; N, 8.57.

EXAMPLE 5

1-Azepan-1-yl-4-((cis)-9-methyl-1,3,4,4a,9,9a-hexahydro-2H-pyrido[3,4-b]indol-2-yl)-2-phenyl-butane-1-one

A solution of benzyl chloroformate (3.80 mL, 26.6 mmol) in 100 mL of anhydrous dimethyl- formamide was added under nitrogen dropwise over two hours to a solution of the material prepared in paragraph 1 of Example 4 (7.64 g, 26.6 mmol) and triethylamine (7.42, 53.2 mmol) in 100 ml of anhydrous dimethylformamide at ice bath temperature. After the addition the reaction was stirred at ice bath temperature for two hours and at room temperature overnight. The reaction was diluted with ethyl acetate, washed multiple times with water, dried ($MgSO_4$) and the solvent removed under reduced pressure to give 5.74g of an oil. Purification of the oil on 450g of silica gel (230-400 mesh) eluting with hexane-ethyl acetate gave 2.04g of a solid. Recrystallization of the solid from isopropyl alcohol gave 1.44g (18%) of the benzyloxycarbonyl derivative of the starting material, mp 88-90 °C.

Elemental Analysis for $C_{19}H_{20}N_2O_2$

Calc'd: C, 74.00; H, 6.54; N, 9.08

Found: C, 73.96; H, 6.54; N, 9.03

Sodium hydride (271 mg of a 60% oil dispersion containing 6.78 mmol) was added in portions under nitrogen to a solution of the material prepared in the preceding paragraph (1.74g, 5.65 mmol) in 20 ml anhydrous dimethylformamide at room temperature. After the addition , the reaction was stirred a room temperature for two hours. Methyl iodide (1.06 ml, 16.95 mmol) was added and the reaction stirred at room temperature overnight. The reaction was diluted with ethyl acetate, washed multiple times with water, dried ($MgSO_4$) and the solvent removed under reduced pressure to give 1.0g of an oil. Purification of the oil on 450g of silica gel (230-400

mesh) eluting with hexane- ethyl acetate gave 850 mg (47%) of the methyl derivative of the starting material as a clear oil, MS m/e 322 [M^+].

Elemental Analysis for $C_{20}H_{22}N_2O_2$

Calc'd: C, 74.51; H, 6.88; N, 8.69

Found: C, 73.35; H, 6.85; N, 8.52

A mixture of the material prepared in the preceding paragraph (800 mg, 2.48 mmol) and 120 mg of 10% Pd/C in 80 ml of ethanol was hydrogenated at room temperature and 40 psi for 17 hours. The catalyst was removed by filtration through celite and the solvent was removed under reduced pressure to give 426 mg (91%) of a brown oil which was used in the next step without purification.

A mixture of the material prepared in the preceding paragraph (382 mg, 2.03 mmol), 1-(azepan-1-yl)-4-chloro-2-phenyl-butan-1-one (568 mg, 2.03 mmol), N,N-diisopropylethylamine (353 µl, 2.03 mmol)and potassium iodide (337 mg, 2.03 mmol) in 15 ml of anhydrous dimethylformamide was stirred under nitrogen at 80°C for five hours. The reaction was partitioned between ethyl acetate and water. The aqueous layer was separated and the organic layer washed multiple times with water. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure to give 739 mg of a brown oil. Purification of the oil on 200 g of silica gel (230-400 mesh) eluting with ethyl acetate-methylene chloride gave 361 mg of an off-white solid. This solid was further purified by trituration with hexane to give 205 mg of a solid. The solid (195 mg, 0.45 mmol) was dissolved in diethyl ether and 452 µl (0.45 mmol) of 1N ethereal HCl was added. The solid formed was collected by filtration and dried under high vacuum to give as an off-white solid the title compound (120 mg, 12%) as a hydrochloride, sesquihydrate, 0.2 diethyl etherate, MS, m/e 431 (M^+ - HCl).

Elemental Analyses for $C_{28}H_{37}N_3O \cdot HCl \cdot 1.5\ H_2O \cdot 0.2\ C_4H_{10}O$

Calc'd: C, 67.84; H, 8.30; N, 8.24

Found: C, 68.09; H, 8.43; N, 8.48

EXAMPLE 6

1-Azepan-1-yl-4-(3, 4-dihydro-1H-pyrazino[1, 2-a]indol-2-yl)-2-phenyl-butan-1-one

A mixture of 1, 2, 3, 4-tetrahydropyrazino [1, 2-a]indole (2.35 g, 12 mmol), 1-(azepan-1-yl)-4-chloro-2-phenyl-butan-1-one (2.72 g, 10 mmol), N, N-diisopropylethylamine (1.7 ml, 10 mmol) and potassium iodide (1.6 g, 10 mmol) in 50 ml of anhydrous dimethylformamide was heated under nitrogen at 80°C for five hours. The reaction was partitioned between ethyl acetate and water. The aqueous layer was separated and the organic layer washed five times with water. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure to five 4.25 g of a brown oil. Purification of the oil on 400 g of silica gel (230-400 mesh) eluting with 30% ethyl acetate-hexane gave 3.70 g (92%) of a yellow foam. The foam (2.0 g) was dissolved in 30 ml of diethyl ether and 5 ml of 1N ethereal HCl was added. The solid formed was collected by filtration, rinsed with diethyl ether and dried under high vacuum. Recrystallization of the solid from ethyl acetate gave the title compound as a light yellow solid, hydrochloride, hemihydrate, 0.233 ethylacetate, mp 145-150°C.

Elemental Analysis for $C_{27}H_{33}N_3O \cdot HCl \cdot 0.5\ H_2O \cdot 0.233\ C_4H_8O_2$

Calc'd: C, 69.66; H, 7.72; N, 8.72

Found: C, 69.91; H, 7.61; N, 8.65

EXAMPLE 7

1-Azepan-1-yl-2-phenyl-4-(3, 4, 10, 10a-tetrahydro-1H-pyrazino[1, 2-a]indol-2-yl)-butan-1-one

A mixture of 1, 2, 3, 4, 10, 10a-hexahydro-pyrazino[1, 2-a]indole (735.9 mg, 4.22 mmol), 1-(azepan-1-yl)-4-chloro-2-phenyl-butan-1-one (1.18 g, 4.22 mmol), N, N-diisopropylethylamine (736 µl, 4.22 mmol) and potassium iodide (701 mg, 4.22 mmol) in 20 ml of anhydrous dimethylformamide was heated under nitrogen at 80°C for five hours. The reaction was partitioned between ethyl acetate and water. The aqueous layer was separated and the organic layer washed five times with water. The

organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure to give 1.64 g of a dark brown oil. Purification of the oil on 400 g of silica gel (230-400 mesh) eluting with ethyl acetate gave 710 mg (40%) of a brown oil. The oil (610 mg) was dissolved in 10 ml of diethyl ether and 1.44 ml of 1N ethereal HCl was added. The solid formed was collected by filtration. The solid on standing turned to a foam which was dried under high vacuum to give the title compound as a light tan foam, hydrochloride, sesquihydrate, 0.1 diethyl etherate, MS m/e 417 M^+.

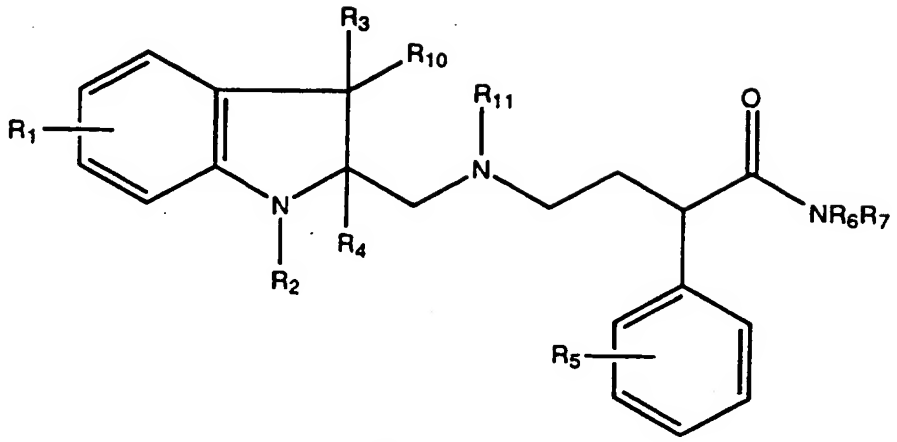
Elemental Analysis for $C_{27}H_{35}N_3O \cdot HCl \cdot 1.5\ H_2O \cdot 0.1C_4H_{10}O$

Calc'd: C, 67.39; H, 8.25; N, 8.60

Found: C, 67.08; H, 8.00; N, 8.35

Claims:

(1) A compound of the formula:



A

where R_1 and R_5 are independently hydrogen, fluorine, chlorine, bromine, iodine, trifluoromethyl, cyano, nitro, CO_2H, C_1-C_6 alkyl, C_2-C_{10} alkenyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkyl, cycloalkylalkyl where the alkyl group is of 1 to 6 carbon atoms and the cycloalkyl group has 3 to 8 carbon atoms, C_3-C_8 cycloalkyloxy, C_2-C_7 alkylcarbonyl, C_2-C_7 alkylcarbonyloxy, C_2-C_7 alkoxycarbonyl, mono- or di-alkylaminocarbonyl in which each alkyl group, independently, contains 1 to 6 carbon atoms, tetrazolyl, -OH, $-(CH_2)_{1-6}OH$, -SH, $-NH_2$ or $-(CH_2)_{1-6}NR_8R_9$ where R_8 is hydrogen, C_1-C_6 alkyl, C_2-C_7 alkylcarbonyl, C_2-C_7 alkoxycarbonyl and R_9 is hydrogen or C_1-C_6 alkyl;

R_{10} and R_{11} together represent dimethylene whilst R_2 is hydrogen or C_1-C_6 hydrogen;

R_3 and R_4 are hydrogen or taken together with the carbon atoms to which they are attached form a double bond;

R_6 and R_7 are independently H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_8 cycloalkyl, cycloalkylalkyl where the alkyl group is 1 to 6 carbon atoms and the cycloalkyl group is 3 to 8 carbon atoms or R_6 and R_7 taken together are polymethylene, which, with the nitrogen atom to which they are attached, form a ring of 3 to 8 atoms; or a pharmaceutically acceptable salt thereof.

(2) A compound of Claim 1 in which R_{10} and R_{11} together represent dimethylene whilst R_2 is hydrogen or C_1-C_6 alkyl.

(3) A compound of Claim 2 in which R_1 and R_5, independently, represent hydrogen, fluorine, chlorine, bromine, trifluoromethyl, CO_2H, C_1-C_3 alkyl, C_1-C_3 alkoxy, C_2-C_4 alkoxycarbonyl, mono- or di-alkylaminocarbonyl in which each alkyl group, independently, contains 1 to 6 carbon atoms, -OH, $-NH_2$ or $-(CH_2)_{1-3}NR_8R_9$ where R_8 is hydrogen or C_1-C_3 alkyl and R_9 is hydrogen or C_1-C_3 alkyl; R_2 is H or C_1-C_3 alkyl; R_3 and R_4 are hydrogen or taken together with the carbon atoms to which they are attached form a double bond; and R_6 and R_7, taken together are polymethylene, which, with the nitrogen atom to which they are attached, form a ring of 5 to 8 atoms; or a pharmaceutically acceptable salt thereof.

(4) The compound of Claim 2 which is 1-azepan-1-yl-2-phenyl-4-(1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl]-butan-1-one or a pharmaceutically acceptable salt thereof.

(5) The compound of Claim 2 which is 1-azepan-1-yl-4-(9-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl]-2-phenyl-butan-1-one or a pharmaceutically acceptable salt thereof.

(6) The compound of Claim 2 which is 1-azepan-1-yl-4-((trans)-9-methyl-1,3,4,4a,9,9a-hexahydro-2H-pyrido[3,4-b]indol-2-yl)-2-phenyl-butan-1-one or a pharmaceutically acceptable salt thereof.

(7) The compound of Claim 2 which is 1-azepan-1-yl-4-((cis)-1,3,4,4a,9,9a-hexahydro-2H-pyrido[3,4-b]indol-2-yl)-2-phenyl-butan-1-one or a pharmaceutically acceptable salt thereof.

(8) The compound of Claim 2 which is 1-azepan-1-yl-4-((cis)-9-methyl-1,3,4,4a,9,9a-hexahydro-2H-pyrido[3,4-b]indol-2-yl)-2-phenyl-butane-1-one

(9) A compound of Claim 1, in which R_2 and R_{11} together represent dimethylene whilst R_{10} is hydrogen.

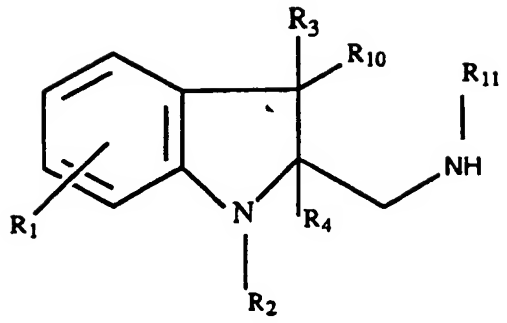
(10) A compound of Claim 9 in which R_1 and R_5, independently, represent hydrogen, fluorine, chlorine, bromine, trifluoromethyl, CO_2H, C_1-C_3 alkyl, C_1-C_3 alkoxy, C_2-C_4 alkoxycarbonyl, mono- or di-alkylaminocarbonyl in which each alkyl group, independently, contains 1 to 6 carbon atoms, -OH, $-NH_2$ or $-(CH_2)_{1-3}NR_8R_9$ where R_8 is hydrogen or C_1-C_3 alkyl and R_9 is hydrogen or C_1-C_3 alkyl; R_3 and R_4 are hydrogen or taken together with the carbon atoms to which they are attached form a double bond; and R_6 and R_7 taken together are polymethylene, which, with the nitrogen atom to which they are attached, form a ring of 5 to 8 atoms; or a pharmaceutically acceptable salt thereof.

(11) The compound of Claim 9 which is 1-azepan-1-yl-4-(3, 4-dihydro-1H-pyrazino[1, 2-a]indol-2-yl)-2-phenyl-butan-1-one or a pharmaceutically acceptable salt thereof.

(12) The compound of Claim 9 which is 1-azepan-1-yl-2-phenyl-4-(3, 4, 10, 10a-tetrahydro-1H-pyrazino[1, 2-a]indol-2-yl)-butane-1-one or a pharmaceutically acceptable salt thereof.

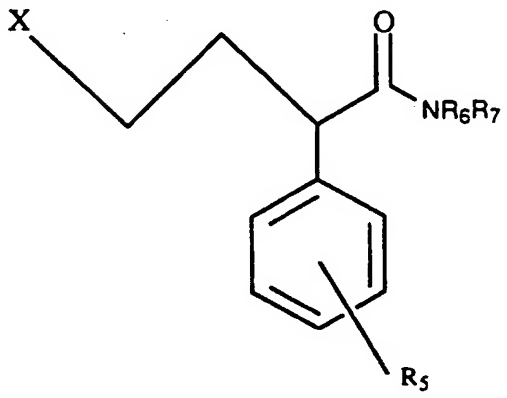
(13) A pharmaceutical composition of matter comprising a compound of as claimed in any one of Claims 1 to 12 in combination or association with a pharmaceutically acceptable carrier.

(14) A process for the preparation of a compound as claimed in Claim 1, which comprises reaction of a compound having formula B:



B

where R_1, R_2, R_3, R_4, R_{10}, and R_{11} are as defined in claim 1 with a compound having the formula C



C

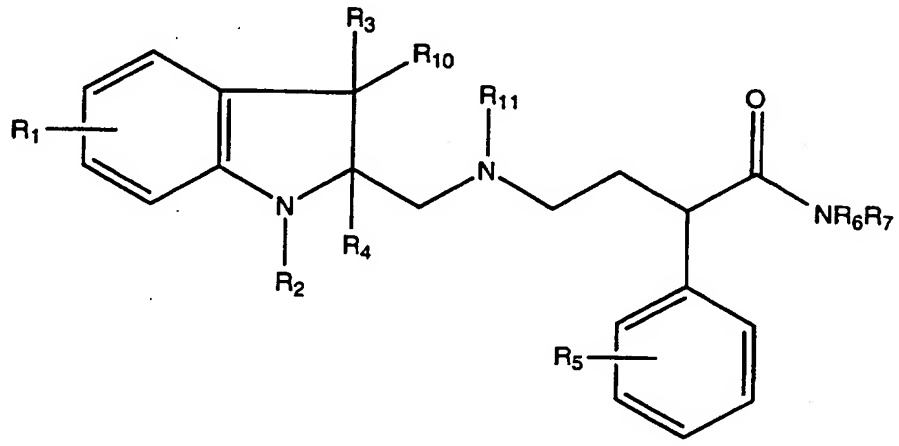
where X is a leaving group and R_5, R_6 and R_7 are as defined in Claim 1 and, where appropriate, converting a resultant compound having the formula A into a pharmaceutically acceptable salt thereof.

(15) A method for relieving symptoms of anxiety which comprises administering a compound as claimed in any one of Claims 1 to 12 in an anxiolytic amount to a mammal in need thereof.

AMENDED CLAIMS

[received by the International Bureau on 19 February 1996 (19.02.96); original claim 1 amended; remaining claims unchanged (1 page)]

(1) A compound of the formula:



A

where R_1 and R_5 are independently hydrogen, fluorine, chlorine, bromine, iodine, trifluoromethyl, cyano, nitro, CO_2H, C_1-C_6 alkyl, C_2-C_{10} alkenyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkyl, cycloalkylalkyl where the alkyl group is of 1 to 6 carbon atoms and the cycloalkyl group has 3 to 8 carbon atoms, C_3-C_8 cycloalkyloxy, C_2-C_7 alkylcarbonyl, C_2-C_7 alkylcarbonyloxy, C_2-C_7 alkoxycarbonyl, mono- or di-alkylaminocarbonyl in which each alkyl group, independently, contains 1 to 6 carbon atoms, tetrazolyl, -OH, $-(CH_2)_{1-6}OH$, -SH, $-NH_2$ or $-(CH_2)_{1-6}NR_8R_9$ where R_8 is hydrogen, C_1-C_6 alkyl, C_2-C_7 alkylcarbonyl, C_2-C_7 alkoxycarbonyl and R_9 is hydrogen or C_1-C_6 alkyl;

R_{10} and R_{11} together represent dimethylene whilst R_2 is hydrogen or C_1-C_6 alkyl or R_2 and R_{11} together represent dimethylene whilst R_{10} is hydrogen;

R_3 and R_4 are hydrogen or taken together with the carbon atoms to which they are attached form a double bond;

STATEMENT UNDER ARTICLE 19

The amendment at page 18 consists in the correction of an obvious error in the definition of the symbols R_2, R_{10} and R_{11}. The error resided in the omission of the words "alkyl or R_2 and R_{11} together represent dimethylene whilst R_{10} is". The correction does not involve the introduction of new matter because the correct definition of the aforesaid symbols can be seen from page 2, lines 9 to 11 and claims 2 and 9 as originally filed.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/US 95/13124

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D487/04 C07D471/04 A61K31/435 A61K31/495
//(C07D487/04,241:00,209:00),(C07D471/04,221:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 302 788 (SYNTHELABO) 8 February 1989 see page 10; claims 1,4	1,13,15
A	JOURNAL OF MEDICINAL AND PHARMACEUTICAL CHEMISTRY, vol.3, no.3, 1961 pages 427 - 440 Z. J. VEJDELEK ET AL 'Synthetic experiments in the group of hypotensive alkaloids. XXI. Chemistry of 1,2,3,4-tetrahydronorharmane-1-carboxylic acid and derivatives' see page 428; example X	1,13,15
A	US,A,4 754 038 (M. A. ABOU-GHARBIA) 28 January 1988 see column 4; claim 1	1,13,15

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
19 January 1996	29.01.96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Voyiazoglou, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/13124

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark : Although claim 15 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/US 95/13124

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,3 641 030 (M. E. FREED ET AL) 8 February 1972 see column 1; claim 1	1,9,13, 15

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interr al Application No
PCT/US 95/13124

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0302788	08-02-89	FR-A-	2619111	10-02-89
		AU-B-	597188	24-05-90
		AU-B-	2044588	09-02-89
		DE-A-	3868301	19-03-92
		JP-A-	1066185	13-03-89
		PT-B-	88206	04-05-95
		US-A-	4977159	11-12-90
US-A-4754038	28-06-88	NONE		
US-A-3641030	08-02-72	US-A-	3736324	29-05-73